



	Experiment title: Supramolecular design of actinide decorporation agents	Experiment number: CH4483
Beamline: BM08	Date of experiment: from: 05/11/2015 to: 09/11/2015	Date of report: 16/02/2016
Shifts: 12	Local contact(s): janeth Lozano rodriguez	<i>Received at ESRF:</i>
Names and affiliations of applicants (* indicates experimentalists): Christophe DEN AUWER* University Nice Sophia Antipolis Florian Lahrouch* University Nice Sophia Antipolis Gaëlle Creff *University Nice Sophia Antipolis Jean Aupiais, CEA DAM-DIF		

Context of the experiment

Exploitation of uranium, widely used, in nuclear plants as combustible with plutonium under mixed oxides form (Mox UO_2^{2+} 91.5 % - PuO_2 8.5 %), or in the nuclear weapons, expose the nuclear workers first and the neighboring populations, in case of leaks or accidents, to potential contamination. In order to eliminate the actinide elements before they are stored in target organs (depending on the element : liver, kidneys, bone), sequestering agents must be quickly injected. In the case of uranyl (UO_2^{2+} , U(VI)), the major part of soluble forms (around 70 %) is quickly remove from the blood system and excreted from the body. The retention part of the absorbed uranyl (around 30 %) is shared between bones (15%) and kidneys (12%)¹. However to date, there is still no ideal sequestering agent, despite the recent concerns in contamination events. Although DTPA (diethylenetriaminepentaacetic acid) raises current interests for an oral or alternative self-administrable form (in USA, SRI is supporting the National Institutes of Health in developing oral forms of Ca-DTPA and Zn-DTPA), it is far from ideal because for instance of its lack of chemical selectivity. Furthermore, DTPA is very ineffective for uranyl complexation ($\log K = 11.8^2$). In order to circumvent this *intrinsic* difficulty, one relatively unexplored strategy is to design functionalized objects that would selectively target the organs of accumulation (liver, kidney, skeleton, lungs in some cases) and with more flexibility than DTPA.

The soluble polymer, polyethyleneimine (PEI), low molecular weight is usually employed in medicinal chemistry as vector, i.e. gene therapy³. Its toxicity is low and its functionalization chemistry is well known. The carboxylate functionalized polyethylene imine (PEI-C) has already been studied for metal complexation applications, for example for the treatment of heavy metal contaminants in waste water⁴. On the other hand, the phosphonate functionalized polyethylene imine (PEI-P) has been used for bone cancer imagery (with Positron Emitting Tomography, PET). In addition to the ability of PEI-P to sequester cations, it also shows a strong tropism for the bone surface. In therapy applications, the non-absorbed complexes in cancerous cells are naturally eliminated through urine⁵.

This is why in our study, we have explored the complexation ability of carboxylate and phosphonate functionalized polyethyleneimine (PEI-C, PEI-P) for uranyl ($\{\text{UO}_2^{2+}\}$). In parallel, functionalization of

¹ E. Ansoborlo et al. *Biochimie* (2006) 88, 1605

² R. J. Abergel et al. *Radiochim. Acta* (2013) 101, 359.

³ R. K. Oskuee et al. *J Gene Med* (2009) 11, 921.

⁴ A. Masotti *Current Analytical Chemistry* (2010) 6, 37

⁵ M. Lbznicek et al. *Appl. Radiat. Isot.* (1994) 45, 949.

mesoporous SiO₂ nanoparticles has also been undertaken but first estimation of uptake capacity is inconclusive. We suspect that functionalization with aminocarboxylate functions has not occurred with the expected rate. This report is therefore based on results obtained with PEI derivatives.

Results

FT-IR data for the commercial PEI and functionalized PEI-C and PEI-P have been recorded and show unambiguously the presence of carboxylate and phosphate functions (the presence of phosphate function is however more difficult to assess because the phosphorous bands overlap with the amine bands). Figure 1 presents a scheme of both polymers with an estimation of polymerization rate. An estimate of the total molecular weight has also been performed for PEI-C (58 kDa) and the functionalization rate has been found to be around 89 % using ¹³C NMR.

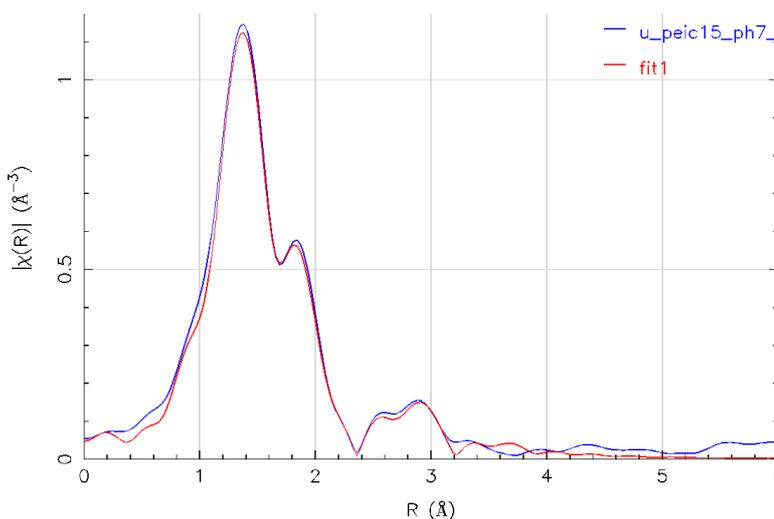
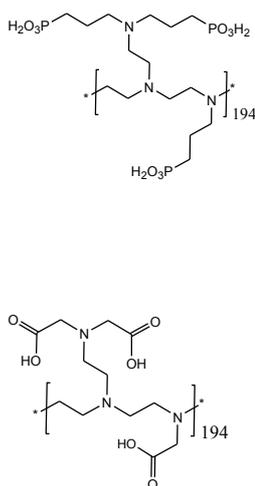


Fig. 1 : drawing of the two polymers PEI-C and PEI-P

Fig. 2 : Fourier transform of the EXAFS spectrum of the sample PEI-C-U, at physiological pH. Blue = experimental, red = fit.

IR spectra have also been recorded in the presence of uranyl and show that complexation occurs. Uptake curves (load curves) are currently being recorded. Several conditions (pH, synthetic conditions) have been explored and EXAFS at the U L_{III} edge (pH 4 and physiological pH) has been recorded in solution around mMolar concentrations.

The Fourier transform of the EXAFS spectrum of the PEI-C complex with uranyl at physiological pH is presented in Fig. 2 with corresponding fit. The best fit data lead to 2 O_{yl} at 1.78 Å (σ^2 : 0.0026 Å²); 6 O_{eq} at 2.36 Å (σ^2 : 0.0152 Å²); 1.7 C_{bid} at 3.43(2) Å, (σ^2 : 0.0065 Å²) and 2.4 C_{mon} at 2.89(4) Å (σ^2 : 0.0045 Å²) ($S_0^2=1.0$, $e_0 = 6.52$ eV, Rfactor = 0.4%). The data clearly show that both bidentate and monodentate carboxylic functions are bound to the uranyl cation. A fit without a mixing of bidentate and monodentate functions did not lead to a satisfactory agreement. The average U-O_{eq} distance is in agreement with data reported in the literature : 2.28 Å for monodentate 2.46 Å for bidentate carboxylates⁶. In order to complement the structural study, a Molecular Dynamics model is also currently being calculated in collaboration with ICSM (CEA Marcoule).

The adjustment of the complex PEI-P with uranyl at physiological pH is more problematic. First of all it shows the presence of clusters of uranyl like in the U-AMP (AMP = adenosine phosphate) complex.⁷ In this structure the cluster is composed 3 uranyl at a distance of 3.92 Å from each other. In the adjustment, the U---U distance is equal to 3.85 Å. But there is also an additional contribution of Br atoms at 2.42 Å that corresponds to the presence of bromopropylphosphonic acid that has been used in the synthesis of the polymer. This impurity that enters the uranyl coordination sphere was unexpected and another synthetic route without bromine is currently being tested. Nevertheless the occurrence of a tri-uranyl cluster with PEI-P is very surprising and must be further explored.

A publication on the synthesis, complexation and characterization of the U-PEI-C is currently being prepared.

⁶ M.A Denecke et al. *J. Alloys and compounds* (1998) 271-273, 123-127.

⁷ Z. Szabó, I. Furó, I. Csöregy, *Journal of the American Chemical Society* (2005), 127, 15236.